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Farmacevtska formulacija

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Alenka Košak
Priimek in ime ter podpis prijavitelja (zastopnika

[Pharmaceutical composition]

Field of the invention

The present invention relates to the pharmaceutical compositions comprising as an active ingredient a substance which is known to appear in various polymorph forms, and to the method of preparing aforesaid composition comprising such substance protected from converting into one or more other polymorph forms. Particularly the present invention relates to the pharmaceutical compositions comprising pravastatin sodium in a crystalline form which exhibits X-Ray diffraction pattern with significant peaks having half-value widths below 2° 2 Theta and the method and manufacturing process to prepare such composition stable.

Prior art

The crystalline pravastatin sodium is disclosed in US 6740775 and forms of pravastatin sodium are disclosed in WO 0143723. Both publications are in their entirety hereby included by reference. It is known that the pravastatin sodium forms D and H as named in WO 0143723 convert to forms A, H, H1, I, J, K as named in WO 0143723 by treating with alcohol. It is also stated, that any polymorph form except B or D would transform into form D as named in WO 0143723 by exposing to 120 °C.

Technical problem

It is advantageous to incorporate into a pharmaceutical composition an active ingredient with an improved crystallinity i.e. having an orderly structure of significant range, which can be characterized by an X-Ray diffraction pattern exhibiting narrow peaks, which is having half-value widths below 2°, preferably below 1°, most preferably below 0.5° 2 Theta.

Among important properties of the active pharmaceutical ingredients are solubility and other important properties which relate to the ease of processing the form into pharmaceutical dosage forms, such as the particle size, density and tendency of a powdered or granulated form to flow and the surface properties that determine whether crystals of the form will adhere to each other when compacted into a tablet. It is desirable to avoid any polymorphic

transitions which may occur during the manufacturing or the solid dosage form and especially during the storage.

Brief description of the drawings

FIG. 1 is a characteristic powder X-ray diffraction pattern of crystalline pravastatin sodium with significant peaks having half-value widths below 2° 2 Theta for which we use in this application the term form LEK and which corresponds to the Figure 2 of the US 6740775.

FIG. 2 is DSC thermogram of pravastatin sodium form LEK

FIG. 3 is a characteristic powder X-ray diffraction pattern of pravastatin sodium form D as named in WO 0143723 and corresponds to FIG. 7 of WO 0143723 for which we use in this application the term form D

FIG. 4 is DSC thermogram of pravastatin sodium form D as named in WO 0143723

Description of the invention

Diffraction pattern is scattering of X-rays from a crystal. It depends on the "long- range" order in the crystal. More disorder means poorer diffraction especially at higher resolution. Not wishing to be bound by any theory it is believed that narrow peaks throughout the scale up to above 30° 2 Theta correspond to the long range orderly crystalline structure while intense peaks at the low 2 Theta values correspond to short range order, also it is contemplated that the extensive broadening of the peaks is attributed to the amorphous structure.

Methods known in the art can be used to prepare a pharmaceutical composition. The pravastatin sodium characterized by an X-Ray diffraction pattern exhibiting narrow peaks, which is having half-value widths below 2°, preferably below 1°, most preferably below 0.5° 2 Theta may be administered in pure form or in a composition, and may be in the form of a powder, granules, aggregates or any other solid form. The compositions of the present invention include compositions for tableting.

Tableting compositions may have in addition to active pharmaceutical ingredient few or many components depending upon the tableting method used, the release rate desired and other factors. For example, compositions of the present invention may contain inactive ingredients

(excipients) which function as such as different fillers, binders, disintegrants, glidants, lubricants and excipients that enhance the absorption of drugs from gastrointestinal tract. Suitable fillers may be selected from microcrystalline cellulose, powdered cellulose, lactose, starch, pregelatinized starch, sucrose, glucose, mannitol, sorbitol, calcium phosphate, calcium hydrogen phosphate, aluminium silicate, sodium chloride, potassium chloride, calcium carbonate, calcium sulphate, dextrates, dextrin, maltodextrin, glycerol palmitostearate, hydrogenated vegetable oil, kaolin, magenesium carbonate, magnesium oxide, polymethacrylates, talc, and others. Preferred fillers are microcrystalline cellulose and lactose. Suitable binders may be starch, pregelatinized starch, gelatine, sodium carboxymethylcellulose, polyvinylpyrrolidone, alginic acid, sodium alginate, acacia, carbomer, dextrin, ehylcellulose, guar gum, hydrogenated vegetable oil, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, glucose syrup, magnesium aluminium silicate, maltodextrin, polymethacrylates, zein. Preferably hydroxypropyl cellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone are used. Suitable disintegrants may be selected from starch, pregelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, cross-linked sodium carboxymrethylcellulose, calcium carboxymethylcellulose, methylcellulose, microcrystalline cellulose, powdered cellulose, polacrilin potassium, cross-linked polivinylpyrrolidone, alginic acid, sodium alginate, colloidal silicon dioxide, guar gum, magnesium aluminium silicate, and others. Preferred disintegrants are sodium starch glycolate, cross-linked carboxymethylcellulose sodium and cross-linked polyvinylpyrrolidone. Suitable glidants may be magnesium stearate, calcium stearate, aluminium stearate, stearic acid, palmitic acid, cetanol, stearol, polyethylene glycols of different molecular weights, magnesium trisilicate, calcium phosphate, colloidal silicon dioxide, talc, powdered cellulose, starch and others. Preferred glidant is colloidal silicilon dioxide. Suitable lubricants may be selected from stearic acid, calcium, magnesium, zinc or aluminium stearate, siliconized talc, glycerol monostearate, glycerol palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, light mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, sodium stearyl fumarate, talc and others. Preferred lubricants are calcium or magnesium stearate and stearic acid. Suitable absorption enhancers may be selected from surface active agents, fatty acids, middle chain glycerides, steroide detergents (salts of bile salts), acyl carnitine and alcanoloil choline (esters of carnitine and choline and fatty acids with middle chain and long chain), N-acyl derivatrives of alpha-amino acids and N-acyl derivatives of non-alpha-amino acids, chitosanes and other mucoadhesive polymers. Especially suitable absorption enhancers are sodium deoxycholate, sodium taurocholate, polisorbate 80, sodium lauryl

sulfate, sodium dodecylsulfate, octanoic acid, sodium docusate, sodium laurate, glyceride monolaurate, stearic acid, palmitinic acid, palmitooleinic acid, glycerilmonooleate, sodium taurocholate, ethylenediaminetetraacetic acid, sodium edentate, sodium citrate, b-cyclodextrine and sodium salicylate.

The solid dosage forms can be prepared by conventional method. Tablet can be for example manufactured by direct compression though wet granulation is another commonly used technique. In wet granulation at least one of the ingredients can be mixed or contacted with liquid and further processed to provide aggregates, the liquid can be partially or completely removed and optionally other or more of the same ingredients may be further added and solid dosage forms manufactured.

Capsules will contain the solid composition within a capsule which may be made of gelatin or other encapsulating material.

Tablets and powders may be coated which may be a conventional or any other for example an enteric coating. The coatings may comprise phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may a tablet comprise a powder or granules with a coating.

In human subjects with normal hepatic function and moderate body weight, a reduction in serum cholesterol levels by administration of solid dosage form of present invention is typically observed with daily dosages of 10, 20, 40 or 80 mg of pravastatin sodium.

In our research work we have investigated the polymorphic transformations of crystalline pravastatin sodium. We have used an improved crystalline form of pravastatin sodium which can be characterized by an X-Ray diffraction pattern exhibiting narrow peaks, which is having half-value widths below 2°, preferably below 1°, most preferably below 0.5° 2 Theta for which we use in this application the term form LEK and which corresponds to the Figure 2 of the US 6740775

Detailed description of the invention

We have investigated the stability of polymorph form of the active pharmaceutical ingredient when granulating with alcohol. Pravastatin sodium in polymorph form that we have used did not convert to other polymorph forms while granulating with an alcohol.

However when granulating with an alcohol the pravastatin sodium admixed with diluent such as microcrystalline cellulose or granulating the pure pravastatin sodium with the alcohol with dissolved binder such as povidone we have in some instances observed complete or partially transformation into form D as named in WO 0143723.

We have further prepared compositions which were binary mixtures of active pharmaceutical ingredient and one excipients. Further we have prepared compositions comprising besides active pharmaceutical ingredient also diluents, binders, disintegrants, lubricants and pigment. The compositions were optionally coated and in some instances observed complete or partially transformation into form D as named in WO 0143723.

Surprising discovery is contrary to the teaching in WO 0143723 where an opposite transformation would be expected. The transformation can not be attributed to the heat, since the granulates were dried at room temperature or at 50° contrary to the required 120° of WO 0143723 which allegedly transforms any other form into form D and applying same drying conditions to all samples not all samples converted.

Our invention is in one aspect the method of stabilizing active pharmaceutical ingredient in an polymorph form susceptible to conversion into other polymorph forms in a pharmaceutical composition, where one of the excipients is a microcrystalline cellulose and the liquid used in preparation of aforesaid pharmaceutical composition is an alcohol or aqueous solution thereof, characterized in that the ratio of active ingredient and microcrystalline cellulose in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 1, preferably above 2 and the ratio of active pharmaceutical ingredient and liquid used in preparation of wet phase used in above preparation is above 2 preferably above 2,5.

Our present invention is especially exemplified in the method of stabilizing crystalline pravastatin sodium present in polymorph form characterized by an X-Ray diffraction pattern

exhibiting narrow peaks. When ethanol or aqueous solution containing ethanol is used preferred mass ratio of pravastatin sodium to microcrystalline cellulose such as Microcel produced by Blanver or Vivapur is at least above 0,5, preferably above 1,25, most preferably above 2 or even above 3 and mass ratio of pravastatin sodium to the liquid should not be as low as 0,8, but should be at least above 1, preferably above 1,6, more preferably above 2, most preferably above 2,5 or higgher.

In another aspect our invention is the method of stabilizing active pharmaceutical ingredient in an polymorph form susceptible to conversion into other polymorph forms in a pharmaceutical composition prepared by wet granulation where one of the excipients is binder such as polyvinylpyrrolidone and that polyvinylpyrrolidone is not dissolved or suspended in the liquid used in preparation of aforesaid pharmaceutical composition.

The preferred active pharmaceutical ingredient is the crystalline form of pravastatin sodium which can be characterized by an X-Ray diffraction pattern exhibiting narrow peaks, which is having half-value widths below 2°, preferably below 1°, most preferably below 0.5° 2 Theta and preferably it is stabilized against precrystalizing which is a conversion into an polymorph form which exhibits broad peaks in X-Ray diffraction pattern, having half-value widths of significant peaks above 2° 2 Theta. Preferably the crystalline form of pravastatin sodium which can be characterized by an X-Ray diffraction pattern substantially as presented on Fig 1 is stabilized against precrystalization into other forms, preferably against precrystallization into form D as named in WO 0143723

Another aspect of our invention is the stabilized pharmaceutical composition comprising the polymorph form of pravastatin sodium which exhibits X-Ray diffraction pattern with significant peaks having half-value widths below 2° 2 Theta characterized in that the polymorph form of pravastatin sodium does not convert to one exhibiting broad peaks in X-Ray diffraction pattern, having half-value widths of significant peaks above 2° 2 Theta. Preferably the stabilized pharmaceutical composition comprise microcrystalline cellulose and the liquid used in preparation of aforesaid pharmaceutical composition is alcohol and it is characterized in that the ratio of pravastatin sodium and microcrystalline cellulose in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 1, preferably above 2 and the ratio of pravastatin sodium and alcohol used in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 2 preferably above 2.5. Most preferably in case pharmaceutical composition comprises binder such as

polyvinylpyrrolidone and that pharmaceutical composition is prepared by wet granulation, the binder is not dissolved or suspended in the liquid used in preparation of aforesaid pharmaceutical composition. Most preferably the stabilized pharmaceutical composition comprises the polymorph form of pravastatin sodium exhibiting the X-ray diffraction pattern substantially similar to one in FIG. 1.

In another aspect the invention is a process for preparation of the stabilized pharmaceutical composition comprising polymorph form of pravastatin sodium which exhibits X-Ray diffraction pattern with significant peaks having half-value widths below 2° 2 Theta preferably exhibiting the X-ray diffraction pattern substantially similar to one in FIG. 1, preferably by wet granulation characterized in that the polymorph form of pravastatin sodium is confirmed by DSC.

Experimental part

When granulating the active pharmaceutical ingredient with absolute ethanol or an aqueous solution of ethanol no conversion of the polymorph form occurred even after drying at temperatures up to 50° in vacuum. However granulation with a granulating liquid comprising a binder did in some experiments induce a partial conversion as summarized in Table 1.

Table 1: List of experiments and polymorph analysis results of granulation of crystalline pravastatin sodium form LEK with ethanol and ethanol solution of PVP

Example No.	**Experiment conditions**	**XRPD results**	**DSC results**
Example 1	15 g pravastatin Na + 15 g ethanol, drying in vacuum at RT, 12 h	**form LEK**	form LEK
Example 2	12.4 g pravastatin Na + 12 g of 20 % PVP solution in ethanol, drying in vacuum at RT, 12 h	**form LEK + trace of form D**	-
Example 3	14.8 g pravastatin Na + 9 g of ethanol containing 6,3 % water, drying in vacuum at 50 °C, 12 h	**form LEK**	-
Example 4	9.9 g pravastatin Na + 9 g of 20 % PVP solution in wet ethanol (4.4 % water), drying in vacuum at 50 °C, 12 h	**form LEK**	-

From the results of the experiments one can conclude that alcohol such as absolute ethanol or aqueous solution thereof does not cause the precrystallization of pravastatin sodium. Polymorphs were identified by characteristic results of the DSC analysis, which compared to classical method of confirming the polymorph forms by X-ray proved simpler but equally reliable for confirming the polymorph form of the active pharmaceutical ingredients which enters into manufacturing of a pharmaceutical composition. DSC method is partially useful for determination of crystalline form of pravastatin sodium in the mixture of pravastatin sodium with other excipients but it is a cheap, fast, useful and reliable method for determination of polymorph form of an active pharmaceutical ingredient.

When granulating with alcohol the binary mixtures of the active pharmaceutical ingredient with excipients such as microcrystalline cellulose, lactose, anhydrous disodium hydrogenphosphate, crosslinked carboxymethylcellulose sodium. The conversion of the polymorph form occurred when using microcrystalline cellulose such as Avicel, Vivapur or Microcel at certain ratios to active pharmaceutical ingredient and was dependant on the amount of granulating liquid used.

Table 2: List of experiments and polymorph analysis results of granulation of crystalline pravastatin sodium form LEK and excipients with ethanol

Example No.	**Experiment conditions**	**XRPD results**
Example 5	12.6 g **Avicel** + 3 g pravastatin Na + 10 g ethanol, drying in vacuum at RT and 50 °C	**form D**
Example 6	12 g **dried Avicel** + 3 g pravastatin Na + 10 g ethanol, drying in vacuum at RT and 50 °C	**form D**
Example 7	3 g **lactose** + 6 g pravastatin Na + 9 g ethanol, drying in vacuum at 50 °C	**form LEK**
Example 8	6 g **Na_2HPO_4** + 5 g pravastatin Na + 9 g ethanol, drying in vacuum at 50 °C	**form LEK**

Example 9	2 g **Ac-Di-Sol** + 10 g pravastatin Na + 11 g ethanol, drying in vacuum at 50 °C	**form LEK**
Example 10	1 g **Texapon** + 10 g pravastatin Na + 11 g ethanol, drying in vacuum at 50 °C	**form LEK**
Example 11	2 g **Avicel** + 4 g pravastatin Na + 9 g ethanol, drying in vacuum at 50 °C	**form LEK + form D**
Example 12	2 g **Avicel** + 4 g pravastatin Na + 3 g ethanol, drying in vacuum at 50 °C	**form LEK**
Example 13	6 g **Avicel** + 6 g pravastatin Na + 3 g ethanol, drying in vacuum at RT	**form LEK**
Example 14	6 g **Vivapur** + 6 g pravastatin Na + 3 g ethanol, drying in vacuum at RT	**form LEK**
Example 15	6 g **Avicel** + 6 g pravastatin Na + 7 g ethanol, drying in vacuum at RT	**form LEK + form D**
Example 16	0,5 g **Avicel** + 0,5 g pravastatin Na, dry mixture, 2 h on 60 °C	**form LEK**

One can conclude that pravastatin sodium precrystallizes to form D at presence of high amount of microcrystalline cellulose and granulating liquid. Pravastatin sodium form Lek is stable if mass ratio of pravastatin sodium and microcrystalline cellulose is higher or equal to 1 : 1 and mass ratio of pravastatin sodium and ethanol is higher or equal to 1 : 0.5.

Excipients (Lactose, anhydrous disodium hydrogenphosphate, crosslinked carboxymethyl-cellulose sodium (Ac-Di-Sol) and sodium lauryl sulfate (Texapon)) and drying temperature do not influence precrystallization of pravastatin sodium at wet granulation with ethanol. Exposure of dry mixture of pravastatin sodium and microcrystalline cellulose for 2 hours at 60 °C does not cause any precrystallization.

On the base of results of binary mixtures granulates for tableting were prepared and we had find out that amount of microcrystalline cellulose in inner phase and the amount of ethanol,

which is used for wet granulation of inner phase influence the precrystallization of active pharmaceutical ingredient. More microcrystalline cellulose is added into the inner phase, more ethanol has to be used for proper technological properties of wet granulate.

Example 17 shows that when 66 % of total Avicel PH 112 was added into the inner phase of granulate (ratio pravastatin sodium : microcrystalline cellulose = 1 : 4.25) the quantity of ethanol for wet granulation was that high that the ratio of pravastatin sodium and ethanol was 1 : 1.25. At that conditions pravastatin sodium has precrystallized to form D.
Example 18 shows that when only 7.7 % of total Avicel PH 112 was added into the inner phase of granulate (ratio pravastatin sodium : microcrystalline cellulose = 1 : 0.5) the quantity of ethanol needed for wet granulation was much lower and the ratio of pravastatin sodium and ethanol was 1 : 0.4. At those conditions no precrystalization occurred.

Above composition proved to be stable on prolonged exposure to moisture and temperature up to 60° C.

Differential Scanning Calorimeter (DSC):

Samples were measured on apparatus Perkin-Elmer Analytical Instruments Pyris 1 DSC. Mass of the samples was 1.5 mg; samples were thermal balanced for 1 minute at 30 °C and then heated from 30 to 200 °C at 10 K/min.

X-Ray powder diffraction (XRPD) analysis:

Samples were measured on apparatus Siemens D-5000 by reflex technique at two conditions:

a. Samples with high amount of pravastatin sodium (more than 30 %): CuKα radiation, range from 2 to 37° 2 theta, step 0.04° 2 theta, integration time 1 second, slots V20 and 0.6 mm.

b. Samples with low amount of pravastatin sodium (less than 30 %): CuKα radiation, range from 3 to 12° 2 theta, step 0.04° 2 theta, integration time 15 second, slots V20 and 0.6 mm.

Examples

a. ***Influence of ethanol, water and polyvinylpyrrolidone K25 (PVP K25) on precrystallization of pravastatin sodium to form D***

Example 1

15 g of pravastatin sodium was added in the vessel and while mixing15 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at room temperature for 12 hours. Dry sample was analyzed with XRPD and DSC. The sample contained crystalline pravastatin sodium form LEK, confirmed by both techniques.

Example 2

12.4 g of pravastatin sodium was added in the vessel and while mixing12 g of 20 % solution of PVP in ethanol was sprayed onto the sample. Granular formation was dried in vacuum at room temperature for 12 hours. Dry sample was analyzed with XRPD and DSC. The sample contained crystalline pravastatin sodium form LEK and little amount of form D, confirmed by XRPD. DSC method was partially useful for determination of crystalline form of pravastatin sodium in the mixture of pravastatin sodium and PVP.

Example 3

14.8 g of pravastatin sodium was added in the vessel and while mixing9 g of 6.3 % solution of water in ethanol was sprayed onto the sample. Granular formation was dried in vacuum at 50 °C for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 4

9.9 g of pravastatin sodium was added in the vessel and while mixing9 g of solution of PVP (20 %) and water (4.4 %) in ethanol was sprayed onto the sample. Granular formation was dried in vacuum at 50 °C for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK

b. *Influence of other excipients (microcrystalline cellulose, lactose, anhydrous disodium hydrogenphosphate, crosslinked carboxymethylcellulose sodium and sodium lauryl sulfate) on precrystallization of pravastatin sodium form LEK to form D*

Example 5

3 g of pravastatin sodium and 12.6 g of Avicel PH 112 was added in the vessel and while mixing10 g of ethanol was sprayed onto the sample. A part of granular formation was dried in vacuum at room temperature and the other part at 50 °C for 12 hours. Both dried samples were analyzed with XRPD. They both contained pravastatin sodium in form D.

Example 6

3 g of pravastatin sodium and 12 g of dried Avicel PH 112 was added in the vessel and while mixing10 g of ethanol was sprayed onto the sample. A part of granular formation was dried in vacuum at room temperature and the other part at 50 °C for 12 hours. Both dried samples were analyzed with XRPD. They both contained pravastatin sodium in form D.

Example 7

6 g of pravastatin sodium and 3 g of Lactose 80 mesh was added in the vessel and while mixing9 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at 50 °C for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 8

5 g of pravastatin sodium and 6 g of anhydrous disodium hydrogenphosphate was added in the vessel and while mixing9 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at 50 °C for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 9

10 g of pravastatin sodium and 2 g of Ac-Di-Sol was added in the vessel and while mixing11 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at 50 °C

for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 10

10 g of pravastatin sodium and 2 g of Texapon was added in the vessel and while mixing11 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at 50 °C for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 11

4 g of pravastatin sodium and 2 g of Avicel PH 112 was added in the vessel and while mixing9 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at at 50 °C for 12 hours. Dry sample was analyzed with XRPD. The sample contained a mixture of crystalline pravastatin sodium form LEK and form D.

Example 12

4 g of pravastatin sodium and 2 g of Avicel PH 112 was added in the vessel and while mixing3 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at 50 °C for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 13

6 g of pravastatin sodium and 6 g of Avicel PH 112 was added in the vessel and while mixing3 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at room temperature for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 14

6 g of pravastatin sodium and 6 g of Vivapur 103 was added in the vessel and while mixing3 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at room temperature for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 15

6 g of pravastatin sodium and 6 g of Avicel PH 112 was added in the vessel and while mixing7 g of ethanol was sprayed onto the sample. Granular formation was dried in vacuum at room temperature for 12 hours. Dry sample was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK and small amount of form D.

Example 16

0.5 g of pravastatin sodium and 0.5 g of Avicel PH 112 was added in the vessel and homogenized. Dry mixture was exposed on 60 °C for 2 hours. Sample was analyzed with XRPD and it contained crystalline pravastatin sodium form LEK.

c. Preparation of granulates of pravastatin sodium with excipients for tableting

Example 17

First phase of granulate contained:

- 32 g Pravastatin Na crystalline form LEK
- 136.6 g Avicel PH 112
- 16.0 g Lactose 80 mesh
- 38.4 g anhydrous disodium hydrogenphosphate
- 5.76 g Ac-Di-Sol
- 1.60 g Texapon

9.6 g PVP K25 was dissolved in 40 g ethanol. Thus prepared solution was sprayed on dry blend of the first phase. Granular formation was dried in vacuum at 50 °C for 5 hours.
To the dried and sieved granulate further components were added:

- 0.24 g pigment brown iron oxide
- 70.8 g Avicel PH 112
- 5.76 g Ac-Di-Sol
- 1.6 g Aerosil 200
- 1.6 g magnesium stearate

The mixture was blended and homogenized. The first phase of granulate (after granulation and drying) was analyzed with XRPD. The sample contained pravastatin sodium form D.

Example 18

First phase of granulate contained:

- 60 g Pravastatin Na crystalline form LEK
- 30 g Avicel PH 112
- 30 g Lactose 80 mesh
- 72 g anhydrous disodium hydrogenphosphate
- 10.8 g Ac-Di-Sol
- 3.0 g Texapon
- 18 g polyvinylpyrrolidone K25

While mixing, 23,7 g of ethanol was sprayed onto dry mixture of above first phase. Granular formation was dried in vacuum at 50 °C for 5 hours.

Into the dried granulate further components were added:

- 0.45 g pigment brown
- 359 g Avicel PH 112
- 10.8 g Ac-Di-Sol
- 3.0 g Aerosil 200
- 3.0 g magnesium stearate

The mixture was blended and homogenized.

The first phase of granulate (after granulation and drying) was analyzed with XRPD. The sample contained crystalline pravastatin sodium form LEK.

Example 19

0.4 g of granulate sample of the firts phase from the previous experiment (Example 18) has been stored in the glass vials. Part of the samples was moistened (1.25 % of water) and the other part was kept dry. Vials were hermetically closed and exposed to the temperature 60 °C. Samples were analyzed with XRPD after 1, 3, 7 and 14 days of storage at 60 °C. In all samples pravastatin sodium did not precrystallize. Tablets prepared according to the composition of previous experiment have been subjected to accelerated stability testing at 60°C for one month,

Claims

1. Method of stabilizing the active pharmaceutical ingredient in an polymorph form susceptible to conversion into other polymorph forms in a pharmaceutical composition, where the excipients comprise microcrystalline cellulose and the liquid used in preparation of aforesaid pharmaceutical composition is alcohol, characterized in that the ratio of active pharmaceutical ingredient and microcrystalline cellulose in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 1 and the ratio of active pharmaceutical ingredient and alcohol used in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 2.

2. Method of stabilizing the polymorph form of pravastatin sodium in a pharmaceutical composition against the conversion into other polymorph form of pravastatin sodium or mixture thereof, where the excipients comprise microcrystalline cellulose and the liquid used in preparation of aforesaid pharmaceutical composition is alcohol, characterized in that the ratio of pravastatin sodium and microcrystalline cellulose in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 1 and the ratio of pravastatin sodium and alcohol used in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 2.

3. Method according to claim 2 where the polymorph form of pravastatin sodium is stabilized against conversion into a polymorph form which exhibits broad peaks in X-Ray diffraction pattern, having half-value widths of significant peaks above 2° 2 Theta.

4. Method according to any one of the claims 2 to 3 where the stabilized polymorph form of pravastatin sodium is characterized by X-Ray diffraction pattern substantially similar to Fig 1.

5. Method according to any one of the claims 2 to 4 where the polymorph form of pravastatin sodium is stabilized against conversion into a polymorph form of pravastatin sodium is characterized by X-Ray diffraction pattern substantially similar to Fig 3.

6. The stabilized pharmaceutical composition comprising the polymorph form of pravastatin sodium which exhibits X-Ray diffraction pattern with significant peaks having half-value widths below 2° 2 Theta characterized in that the polymorph form of pravastatin sodium is stabilized against converting into one exhibiting peaks in X-Ray diffraction pattern, having half-value widths of significant peaks above 2° 2 Theta.

7. The stabilized pharmaceutical composition according to previous claim further characterized in that the composition comprises microcrystalline cellulose and that the liquid used in preparation of aforesaid pharmaceutical composition is alcohol, characterized in that the ratio of pravastatin sodium and microcrystalline cellulose in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 1 and the ratio of pravastatin sodium and alcohol used in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 2.

8. The stabilized pharmaceutical composition according to any one of claims 6 to 7 comprising the polymorph form of pravastatin sodium exhibiting the X-ray diffraction pattern substantially similar to one in FIG. 1.

9. The stabilized pharmaceutical composition comprising the polymorph form of pravastatin sodium exhibiting the X-ray diffraction pattern substantially similar to one in FIG. 1 prepared by a process where at least one step includes addition of a liquid and the composition comprises microcrystalline cellulose and the liquid used in preparation of aforesaid pharmaceutical composition is alcohol, characterized in that the ratio of pravastatin sodium and microcrystalline cellulose in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 1 and the ratio of pravastatin sodium and alcohol used in preparation of wet phase used in preparation of aforesaid pharmaceutical composition is above 2.

10. Process for preparation of the stabilized pharmaceutical composition comprising polymorph form of pravastatin sodium exhibiting the X-ray diffraction pattern substantially similar to one in FIG. 1 characterized in that the polymorph form of pravastatin sodium is confirmed by DSC analysis.

Abstract

Stabilized pharmaceutical composition comprising the polymorph form of pravastatin sodium which exhibits X-Ray diffraction pattern with significant peaks having half-value widths below 2° 2 Theta which does not convert to other polymorph forms and the method of stabilization.

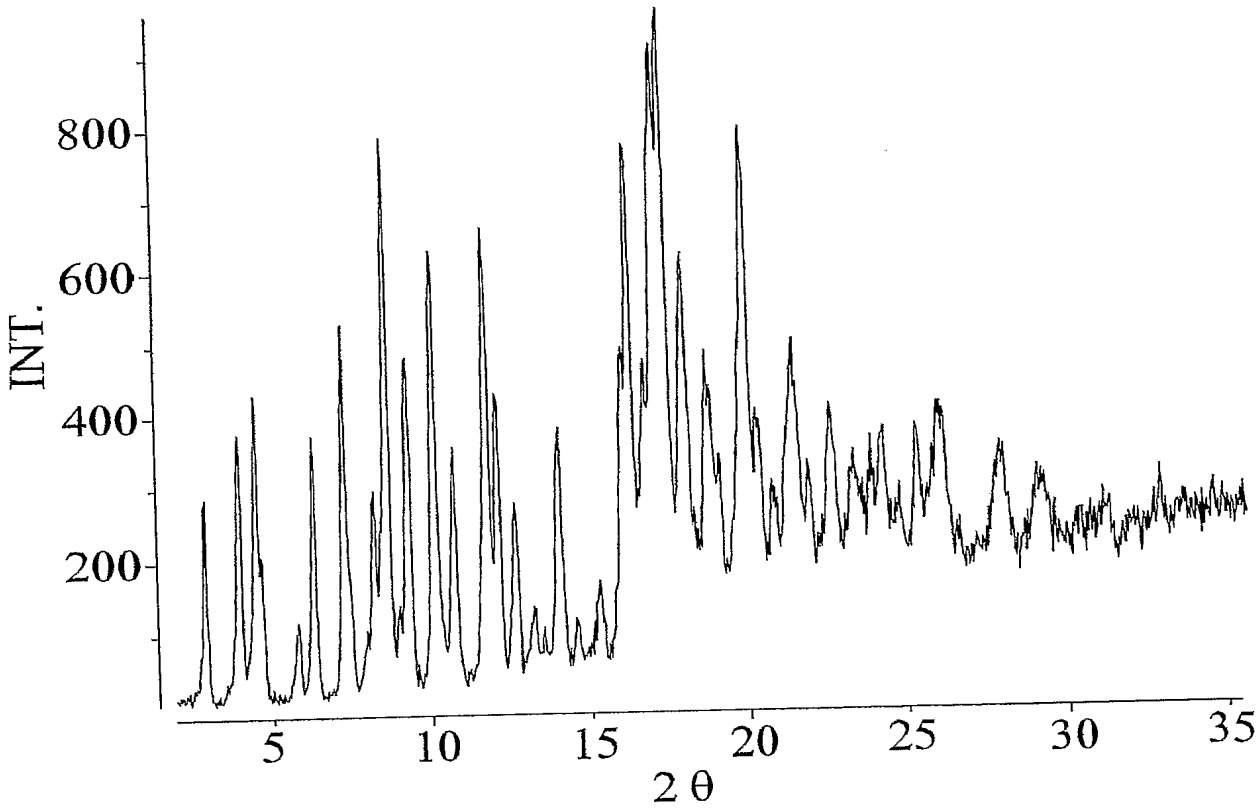

FIG. 1

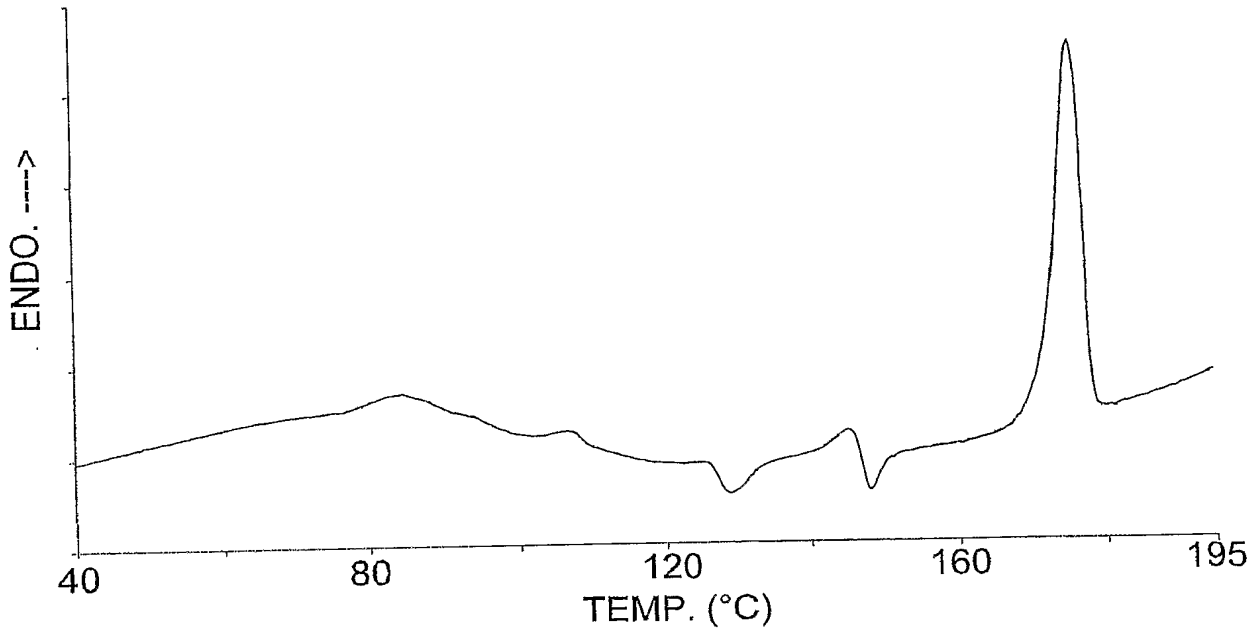

FIG. 2

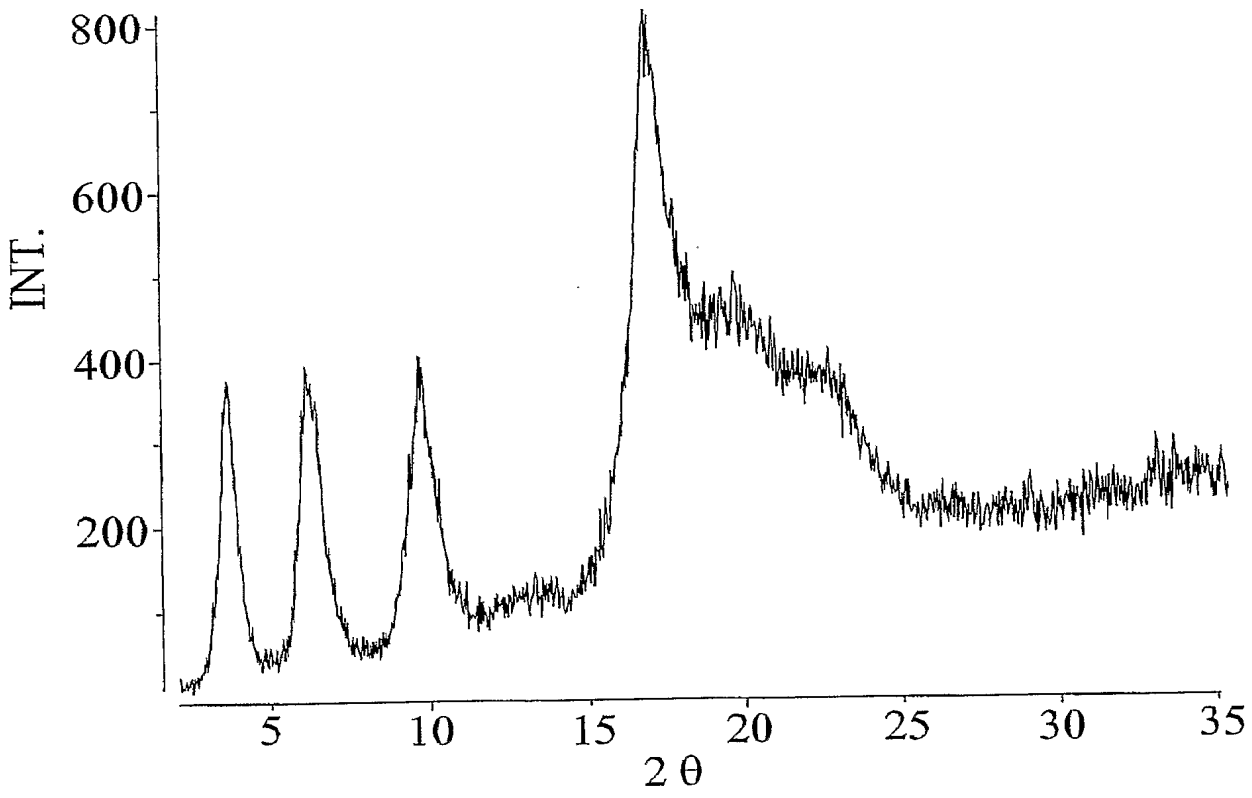

FIG. 3

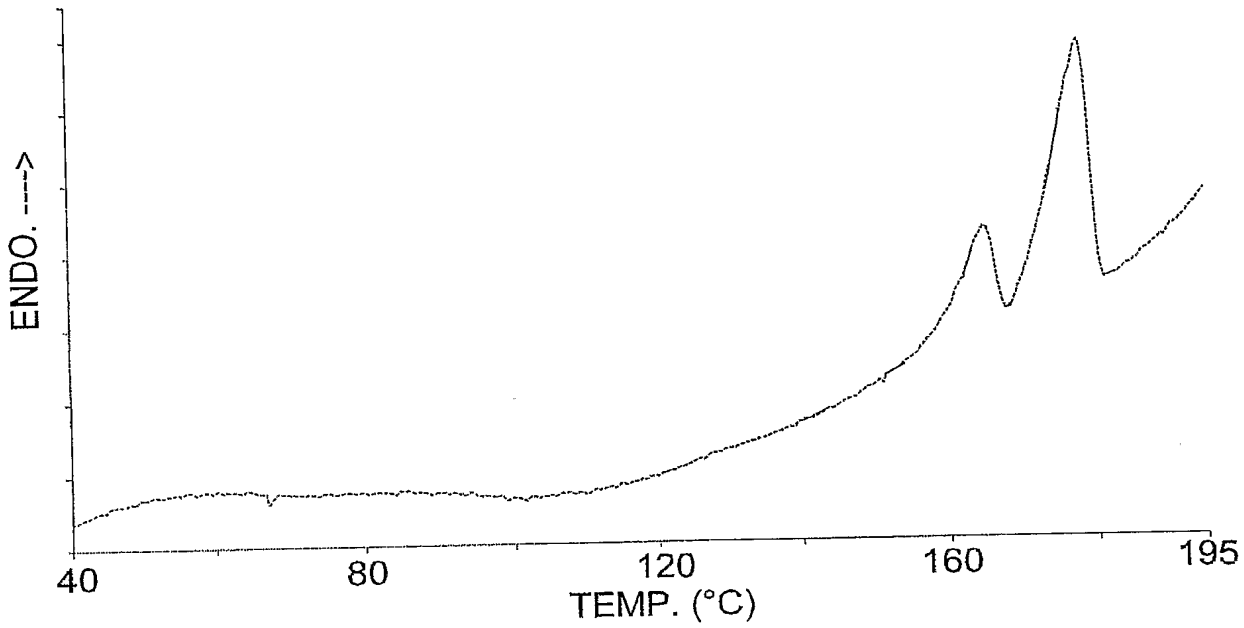

FIG. 4